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EXAMINER: MILNE, A

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18N2/0806

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 4-8-96 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-22 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-22 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

Claims 1-22 are currently pending in U.S. Patent Application Number 08/217,324. The amendment filed 4-8-96 has been entered and carefully considered.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and use the invention and failing to provide an enabling disclosure. Applicant's claims are broadly directed to devices and methods for the implantation of genetically modified cells into the vascular system of a human (or animal) "patient" for therapeutic purposes. The invention as claimed encompasses the implantation of smooth muscle cells expressing any "gene of interest" into any animal such that a recombinantly expressed gene product can be delivered as a therapeutic. This is further elaborated in the specification to include "enzymes, cytokines, receptors, hormones, growth factors, coagulation factors, and the like" (page 4, lines 30-32). There is insufficient guidance in the specification for a skilled artisan to recombinantly express in vivo such a gene encoding one of these products for therapeutic

use, at a therapeutic level, with proper regulation of expression.

Applicants' refer to U.S. Patent 5,399,346 (issued to Anderson et al.) that emphasized the general predictability of gene therapy. For example, page 3 of the instant amendment states:

> "To the best of his information and belief, the RAC does not approve a human gene therapy protocol unless there is a reasonable expectation of efficacy...".

Primarily, it must be noted that each application submitted to the U.S. Patent Office is examined on its own merits regarding the direction and guidance supplied in the specification.

Secondly, the statement provided above indicates that unless the RAC has a strong belief that the protocol might work, approval will not be granted to conduct the research. Such is not correlatable to the standards set forth to establish enablement of an invention, insofar as 35 U.S.C. § 112, first paragraph is concerned. Applicant appears to argue that the invention is credible. However, the credibility of the claimed invention is not part of the rejection of record. Credibility is a rejection under 35 U.S.C. 101. Further, the guidelines as published, Federal Register (60 FR 36263, July 14, 1995), clearly state that a rejection under 35 U.S.C. 112 "how to use" is entirely proper absent a rejection under 35 U.S.C. 101. The

rejection of record is under 35 U.S.C. 112, "how to use". While the artisan may consider the invention credible, this is not the same as having an enabling disclosure at the time of filing. A utility for the claimed invention can be considered credible, and thus 101 is satisfied, while the specification does not teach how to use the claimed invention. Whether or not RAC approval has been obtained for a certain project does not have a specific bearing on the claimed invention insofar as a lack of enablement is concerned. The basic argument reiterated here, is that the specification does not provide sufficient guidance to the artisan for a method of transferring *in vivo* a therapeutic gene into target cells such that a therapeutic effect is achieved and that the results would be deemed correlatable to the use of the instant invention in any and all patients.

Applicants further intend that there is no requirement that they enable all forms of human gene therapy as certain claims of the instant invention recite a "device".

This argument is not deemed persuasive because the disclosed use of the device in the specification is in a therapeutic paradigm, therefore, to satisfy the standards of enablement, applicants are required to teach "how to make" and "how to use" the claimed invention. Given the exceedingly high level of unpredictability in the art of gene therapy at the time of the instant invention, it is not clear that the skilled artisan could achieve a therapeutic effect using the claimed device without

having to undertake undue experimentation.

Applicants also intend that the disclosed working examples employing the lac Z gene are entirely appropriate as a model for expressing a potentially useful therapeutic protein. Applicants intend that said gene was used in the baboon model and such research was submitted and published in peer-reviewed scientific journals. These arguments are not deemed persuasive.

Primarily, publication of research is not grounds for satisfying the requirements of enablement of a claimed invention. While the references, indicated on page 7 of the amendment, have been considered, they are not sufficient guidance regarding how to use the claimed invention.

Applicants' submit on pages 8 and 9 of the amendment that the instant invention does not lie within the vectors themselves but rather in the device and methods of implanting vascular smooth muscle cells and therefore, that the publications such as Jolly, submitted in the first action, pertain merely to problems associated with such vectors which, as indicated by applicants, are currently being optimized and therefore, the examiner has not addressed the unpredictability of the claimed invention.

The first office action clearly discusses the problems associated with the components, i.e. vectors and such, that make up portions of the claimed invention. There is no information in the specification that would guide one of ordinary skill in the art to transduce the insulin or proinsulin gene into appropriate

target cells such that the level of expression necessary to treat the disease would be sufficient as a treatment. No information is provided regarding the regulation of insulin expression in response to physiological signals. In addition, this diabetes treatment would not be applicable to patients whose disease is attributable to a lack of insulin receptor molecules rather than insufficient insulin secretion.

The working example in the specification as filed describes the transfer of the lac Z gene, which does not code for a therapeutic compound, and the PNP (purine nucleotide phosphorylase) gene, which does not require precisely regulated expression for therapeutic use. No long-term study data is presented to show the existence or duration of therapeutic levels of protein production. The transduction and expression of the lacZ gene in the animal model presented is not correlatable to the transduction and expression of a therapeutic gene. A skilled artisan would not be inclined to accept short-term expression of a non-therapeutic gene at an undefined expression level as evidence that the claimed invention can treat a diseased patient with a reasonable expectation of success. Likewise, transduction and short-term expression of the PNP gene is not sufficient evidence to convince a skilled artisan that the invention can be successfully used to supply a therapeutic level of a secreted product (such as erythropoietin) or a product requiring strict regulation (such as insulin).

In the invention as claimed, the cells may be transduced by any method, including retroviral, adenoviral and non-viral systems. In the working examples, autologous smooth muscle cells are transduced by a retroviral vector. There are characteristics of each vector system that would contribute to the unpredictability of using the claimed invention as well as limiting its therapeutic utility. The insert size of retroviral vectors is limited to about 8kb, making the retroviral expression of a large gene (such as Factor VIII) impossible with a retroviral system. Further evidence of the unpredictable nature of recombinant delivery of therapeutic genes is taught by Jolly, who teaches that "it is worth noting that building retroviral vectors is still a mixture of art and science. Many creative ideas require multiple design attempts before performing anywhere close to desired" (page 53). Of import to applications where regulated expression is necessary, Jolly adds that "tissue-specific promoters can be successfully incorporated into vectors, but in our experience about one of five alternative designs will behave satisfactorily. It has gradually become apparent that, in general, as the complexity of design increases, the corresponding vector titers usually (but not always) decrease" (page 53). Anderson (Human Gene Therapy, Volume 5, pages 281-282) also addresses this limitation, writing on page 281 that

> Unfortunately, we are still woefully ignorant of the regulatory mechanisms that control gene expression in

> primary cells in vivo. Vectors for gene therapy are, to a certain extent, hit or miss. Viral promoters work well in culture so that many vectors are made using the viral vector's own promoters or are made with SV-40, CMV, or other viral regulatory sequences. Unfortunately, we know that many viral promoters are shut off in primary cells in vivo, but studies using human regulatory sequences are very preliminary.

Other considerations for the use of retroviral vectors include transcriptional shut-off, leading to short term in vivo expression, generally low expression levels (compared to adenoviral systems, for example), and the possibility of insertional mutagenesis leading to tumorigenesis. Adenoviral vectors provide high expression levels but duration is limited (2-6 weeks); they have the additional limitation of inducing a strong immune response that results in inflammation and reaction against repeated administrations. Non-viral systems are limited by transduction efficiency and the inability to integrate into the genome, resulting in transient gene expression. Since long-term, high level expression is necessary for the claimed invention to be therapeutically successful, guidance must be presented to allow one of ordinary skill to choose and evaluate vector constructs in light of the parameters described above.

The working example presented results of the transduction of smooth muscle cells obtained from a baboon, their seeding (with endothelial cells) on a synthetic graft, and the implantation of the graft into the vascular system of the animal. The invention as claimed is directed to the treatment of disease in any animal,

including human beings, using the claimed devices and methods. Ledley et al. reviews somatic gene therapy, and states (on page 79) that

> While animal experiments are useful for assessing specific aspects of gene transfer, there is no data explicitly supporting the contention that animal experiments can presage the outcome, efficacy, or safety of human applications. The details of anatomy, cell biology, genetics, and immunology of other species do not duplicate the vicissitudes of human biology, particularly when considering retroviral vectors whose infectivity, tropism, and pathology is naturally species specific.

Of particular import are species differences in the efficiency of tissue culture, transduction and expression of human smooth muscle cells, compared to the results presented in the animal model. In addition, the animal experiments were conducted on a small sample size and were not directed toward treatment of disease. Therefore it is not likely that the animal studies presented would be accepted by the skilled artisan as support for the claimed subject matter.

It is therefore concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or guidance presented, the lack of correlatable working examples, the nature of the invention, the state of the prior art with its recognized unpredictability, and the breadth of the claims, it would require undue experimentation for others skilled in the art to practice the invention.

Claims 1-22 stand rejected under 35 U.S.C. § 112, first

paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-4, 8-11, 13, and 16-20 stand rejected under 35 U.S.C. § 103 as being unpatentable over Zalewski et al. (WO 93/15609 in view of Nabel et al.(U.S. 5,328,470) and Anderson et al.(WO 90/224,525).

The Zalewski et al. reference discloses methods and kits with devices employing interferon gene therapy for the treatment of vascular disorders. More specifically, the reference discloses transformation of smooth muscle cells on page 8 using various gene transfer methodologies. Further, page 9 of the references discloses the use of implant devices to hold and contain said vascular smooth muscle cells.

The Nabel reference discloses the in situ transduction of endothelial and smooth muscle cells of the arterial wall, or the deposition of cells transduced ex vivo, using a catheter to deposit the cells or appropriate gene transfer vehicle (pages 6-8, see "II: Introduction of cells expressing normal or exogenous proteins into the vasculature"). Nabel discloses the use of the invention to deliver insulin (page 5, line 30), or anticoagulant factors such as urokinase (page 11, line 46-49). Nabel thus discloses in situ gene transduction of smooth muscle cells for therapeutic benefit, but does not disclose a vascular graft containing transduced smooth muscle cells as the method of delivering the gene product of interest.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a synthetic vascular graft to transplant endothelial and smooth muscle cells into a blood vessel as disclosed by Zalewski et al., and to substitute genetically modified for unmodified cells, based on the teaching of the Nabel reference to genetically modify cells of the arterial wall for therapeutic purposes.

Anderson discloses a vascular graft coated with genetically-modified autologous endothelial cells, and further discloses the use of this invention to deliver erythropoietin, Factor IX, G-CSF and GM-CSF proteins, among others. Anderson does not disclose the inclusion of transduced vascular smooth muscle cells in the

graft, which would be obvious to one of ordinary skill in the art based on the Zalewski et al. reference, which includes smooth muscle cells in its graft, and the Nabel reference, which teaches the desirability of vascular smooth muscle cells as a target for gene therapy.

Any rejection not reiterated in this action is hereby considered withdrawn in light of the amendment filed 4-8-96.

Any inquiry concerning this communication from the examiner should be directed to Andrew Milne, whose telephone number is (703) 308-4213. The examiner can normally be reached from 7:00 to 4:00 (Eastern Standard Time) Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached at (703) 308-3153. The fax number for art unit 1804 is (703) 308-0294.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Andrew Milne
8-1-96

JACQUELINE M. STONE
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